Why Do Black Americans Have a Higher Risk of Pancreatic Cancer than White Americans?

Debra T. Silverman,[1] Robert N. Hoover,[1] Linda M. Brown,[1] G. Marie Swanson,[2] Mark Schiffman,[1] Raymond S. Greenberg,[3] Richard B. Hayes,[1] Keith D. Lillemoe,[4] Janet B. Schoenberg,[5] Ann G. Schwartz,[6] Jonathan Liff,[7] Linda M. Pottern,[8] and Joseph F. Fraumeni, Jr.[1]

Background. For several decades, the incidence of pancreatic cancer has been 50% to 90% higher among blacks than among whites in the United States. The purpose of this study was to identify risk factors that may contribute to this racial disparity. **Methods.** We conducted a population-based case-control study of pancreatic cancer diagnosed in Atlanta (GA), Detroit (MI), and 10 New Jersey counties from August 1986 through April 1989. In-person interviews were exclusively with subjects (526 cases and 2153 population controls), rather than with next of kin. **Results.** The determinants of the higher incidence of pancreatic cancer among blacks than among whites differed by sex. Among men, established risk factors (ie, cigarette smoking, long-term diabetes mellitus, family history of pancreatic cancer) account for 46% of the disease in blacks and 37% in whites, potentially explaining all but 6% of the excess risk among blacks. Among women, however, other factors appear to contribute to the racial disparity, notably moderate/heavy alcohol consumption (>7 drinks per week) and elevated body mass index (above the first quartile). When these less accepted risk factors were combined with the established risk factors, 88% of the disease in black women and 47% in white women were explained, potentially accounting for all of the excess risk among blacks in our female study population. **Conclusions.** Among men, the established risk factors (mainly cigarette smoking and diabetes mellitus) explain almost the entire black/white disparity in incidence. Among women, however, other factors appear to contribute to the racial disparity, notably moderate/heavy alcohol consumption and elevated body mass index. In the absence of these factors, pancreatic cancer incidence rates among blacks probably would not exceed those among whites of either sex. (EPIDEMIOLOGY 2003;14:45–54)

Key words: race, cigarette smoking, alcohol consumption, body mass index, diabetes mellitus, socioeconomic factors, pancreatic neoplasm.

For several decades, the incidence of pancreatic cancer has been consistently higher in blacks than in whites in the United States.[1] In 2002, pancreatic cancer will rank fifth among both blacks and whites

From the [1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; [2]formerly with the Michigan Cancer Foundation (renamed the Barbara Ann Karmanos Cancer Center), Detroit, MI; [3]formerly with the Division of Epidemiology, Emory University School of Public Health, Atlanta, GA; [4]Department of Surgery, The Johns Hopkins School of Medicine, Baltimore, MD; [5]formerly with the Cancer Epidemiology Services, New Jersey Department of Health and Senior Services, Trenton, NJ; [6]Barbara Ann Karmanos Cancer Center, Detroit, MI; [7]Division of Epidemiology, Emory University School of Public Health, Atlanta, GA; and [8]formerly with National Cancer Institute, Bethesda, MD.

Address correspondence to: Debra T. Silverman, Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Executive Plaza South, Room 8108, Bethesda, MD 20892; silvermd@mail.nih.gov

in U.S. cancer mortality, accounting for nearly 30,000 deaths.[2] In 1995–1999, the average annual age-adjusted incidence rates were 16.6/100,000 for blacks and 10.7/100,000 for whites.[2] Reasons for this 55% excess risk among blacks are unclear. Pancreatic cancer incidence rates among blacks living in Africa appear to be low in comparison to those among African-Americans,[3–5] suggesting that lifestyle or other environmental factors contribute to the racial disparity in risk in the United States.

In the late 1980s, we conducted a population-based case-control study of pancreatic cancer in black and white Americans to identify reasons for the excess risk among blacks. In previous reports from this study, the effects of cigarette smoking, alcohol drinking, dietary/nutritional factors, medical conditions and family history of pancreatic cancer were examined.[6–9] In particular, cigarette smoking, long-term diabetes mellitus and a positive family history were identified as risk factors for pancreatic cancer. Although causal relations are un-

clear, other factors that appeared to contribute to risk include heavy alcohol consumption, obesity, moderate/high caloric intake, less frequent intake of cruciferous vegetables and cholecystectomy. The purpose of the present analysis is to identify the factors that independently contribute to the excess risk among blacks, and the extent to which these factors may explain the black/white difference in incidence rates. The role of socioeconomic variables (*eg*, income, education, marital status) is also evaluated as a potential contributor to the racial disparity.

Methods

We conducted a population-based case-control study of selected cancers that occur excessively in blacks compared with whites (*ie*, cancers of the pancreas, prostate and esophagus, and multiple myeloma) in three areas of the United States. One general population control group was the source of controls for all four cancer sites.

The case series in this analysis consisted of all cases of carcinoma of the exocrine pancreas (International Classification of Diseases for Oncology code = 157) first diagnosed from August 1986 to April 1989 among 30–79-year-old residents of geographic areas covered by population-based cancer registries located in Atlanta (DeKalb and Fulton counties), Detroit (Macomb, Oakland and Wayne counties), and New Jersey (10 counties). To ensure the population-based nature of the case series and the completeness of case ascertainment, we initially included all cases with reported pancreatic cancer regardless of the presence of tissue confirmation. Because about 15% of the cases lacked tissue confirmation, an in-depth medical chart review was conducted to determine the accuracy of diagnosis. Based on this review, we excluded 5.5% of identified pancreatic cancer patients because they were found to be "unlikely" to have pancreatic cancer. Additional details regarding the chart review have been reported previously.[10]

Because pancreatic cancer is a rapidly fatal disease, death was a major reason for nonparticipation. Despite our emphasis on identifying and interviewing patients at home as quickly as possible (median time from diagnosis to interview was 7 weeks), 471 of the 1153 patients initially identified for study died before the interview could be conducted. Of the 682 surviving patients identified for study, we interviewed 526 patients (percentage interviewed = 75% for whites and 81% for blacks).

To determine the comparability of those who died with those who lived long enough to be interviewed, we conducted interviews with next of kin of a sample of 325 deceased cases. The next-of-kin interview included only broad categorical questions that next-of-kin respondents have been shown to answer reliably.[11–12] For most questions, the pattern of responses from next of kin of deceased cases was similar to that from patients who were interviewed personally.[6–9]

We randomly selected the control series from the general population of the study areas, frequency matching controls to the expected age-race-sex distribution of cases of all four types of cancer combined in each study area. Control subjects age 30–64 years were chosen by random digit dialing of telephone numbers.[13] Eighty-six percent of all households contacted provided a household census that served as the sampling frame for selection of control subjects under 65 years of age. Of the 1568 control subjects selected from these households, we interviewed 1227 (percentage interviewed = 78% for whites and 78% for blacks). Control subjects age 65–79 years consisted of a stratified random sample drawn from the Centers for Medicare and Medicaid Services rosters of the population age 65 or older in each study area. Of the 1232 older control subjects selected, we interviewed 926 (percentage interviewed = 78% for whites and 73% for blacks).

Subjects were usually interviewed at home by interviewers who were not informed of either the case or control status of the subject or the hypotheses under investigation. Written informed consent to participate in the study was obtained from each subject before initiating the interview. The questionnaire was designed to obtain detailed information on smoking habits, alcohol intake, diet and nutritional factors, medical conditions, family history of cancer, usual occupation and socioeconomic status (*ie*, education, annual family income at the time of the interview and the number of individuals supported by that income, and marital status). We also queried subjects about their usual adult height and weight, which was used to compute the body mass index (BMI; kg/m^2 for men, $kg/mg^{1.5}$ for women).[14] The study was reviewed by the National Cancer Institute Special Studies Institutional Review Board.

We used the odds ratio (OR) to quantify the effects of potential risk factors (*eg*, income, education and marital status) on pancreatic cancer risk. ORs and 95% confidence intervals (CIs) were estimated by unconditional logistic regression analysis.[15–16] Statistical models included terms for exposure, the matching factors (*ie*, age at diagnosis/interview, race [when appropriate], sex [when appropriate] and study area), as well as terms for potential confounding variables (*ie*, cigarette smoking, moderate/heavy alcohol consumption, diabetes mellitus, cholecystectomy, moderate/high BMI, moderate/high caloric intake, less frequent cruciferous vegetable intake, low income and marital status). To test for trend, we computed the Wald statistic. When appropriate, the exposure variable was treated as continuous in the model by entering the median value among the controls for each level of the categorical variable.

TABLE 1.   Association of Income, Education and Marital Status with Pancreatic Cancer, by Sex and Race

	Men								Women							
	White				Black				White				Black			
Risk Factor	No. of Cases	No. of Controls	OR*	95% CI	No. of Cases	No. of Controls	OR*	95% CI	No. of Cases	No. of Controls	OR*	95% CI	No. of Cases	No. of Controls	OR*	95% CI
Income†																
≥$25,000	63	389	1.0		12	165	1.0		47	170	1.0		11	49	1.0	
$10,000–24,999	71	237	1.5	1.0–2.3	30	233	1.9	0.9–4.2	48	134	0.9	0.5–1.6	34	110	1.3	0.6–3.0
<$10,000	19	53	1.8	0.9–3.4	28	158	2.7	1.2–6.1	30	65	1.3	0.6–2.7	44	166	0.8	0.3–1.9
			P = 0.022‡				P = 0.013‡									
Education§																
>High school	56	337	1.0		13	117	1.0		37	146	1.0		16	54	1.0	
High school	57	207	1.2	0.8–1.9	17	132	1.1	0.5–2.3	64	164	1.1	0.6–1.8	28	107	0.9	0.4–2.0
<High school	51	188	0.9	0.5–1.5	48	347	1.1	0.5–2.3	41	111	0.9	0.5–1.6	50	186	0.8	0.4–1.7
Marital status‖																
Married	133	589	1.0		43	388	1.0		82	268	1.0		30	151	1.0	
Widowed, separated, divorced	20	110	0.7	0.4–1.1	28	185	1.3	0.7–2.2	55	134	1.2	0.7–2.0	60	178	1.9	1.1–3.3
Never married	11	39	1.2	0.6–2.5	7	23	2.3	0.9–6.2	6	22	1.1	0.4–3.1	4	18	1.2	0.3–4.4

* ORs adjusted for age at diagnosis/interview, study area, cigarette smoking, heavy alcohol drinking, diabetes mellitus, cholecystectomy, obesity, total caloric intake, and cruciferous vegetable intake.
† Annual income at time of interview. ORs also adjusted for marital status.
‡ *P*-value for test of linear trend.
§ ORs also adjusted for income and marital status.
‖ ORs also adjusted for income.

We used the population attributable risk (PAR) as an analytic tool to quantify the proportion of the black excess in risk that may be attributable to a specific risk factor or combination of risk factors (summary PAR). Race- and sex-specific PARs were computed by the method of Bruzzi et al.,[17] and two-sided 95% CIs by the method of Benichou and Gail[18]; PARs and their CIs were adjusted for the same potential confounding variables as the ORs. This approach to PAR estimation is based on unconditional logistic regression. For meaningful PAR estimation, we defined cutpoints for exposure to capture the observed increase in risk associated with that variable or variables, which may have differed by sex. When the shape of the dose-response curve for an exposure differed for men and women, we used the cutpoints for the exposure that best expressed the increased risk in each sex. Within each sex, however, race-specific PARs were based on the same exposure cutpoints because the main comparison in this analysis was between the PARs for blacks and those for whites.

Some interviewed subjects were excluded from analysis for the following reasons: the presence of pancreatic cancer judged unlikely (16 cases), histologic diagnosis of islet cell carcinoma (10 cases), no medical record available for review (6 cases), unsatisfactory interview (1 case and 7 controls), and data not ascertained for one or more key analytic variables (14 cases and 41 controls). In addition, 45 cases and 132 controls with unreliable dietary histories (ie, subjects with extremely low or high amounts of food consumption) were excluded from all PAR analyses because many PAR analyses included dietary factors as exposure variables. Thus, the PAR analyses were based on first-person interviews with 434 cases

diagnosed with carcinoma of the exocrine pancreas and 1973 population controls.

Results

Socioeconomic Status

We examined pancreatic cancer risk according to several measures of socioeconomic status: income, education and marital status (Table 1). Among men, a substantial inverse trend in risk with decreasing income was apparent in both blacks and whites (*P* value for trend = 0.013 and 0.022, respectively). Estimates of risk were higher for blacks than whites at each level of income, with ORs peaking at 2.7 (CI = 1.2–6.1) for blacks and 1.8 (0.9–3.4) for whites with a family income of less than $10,000 per year, after adjustment for potential confounding variables (including number of family members supported by that income). In contrast, number of years of education completed appeared unrelated to risk in both black and white men. We also examined an occupation-based measure of socioeconomic status (data not shown). Patterns of risk were similar to those observed for income although somewhat weaker, suggesting that income rather than occupation *per se* was more strongly related to risk. A separate analysis of data collected on usual occupation suggested that occupational exposures play a relatively small role in the etiology of pancreatic cancer (data not shown). In the evaluation of marital status, being never married appeared related to an elevated risk in black men (OR = 2.3; 0.9–6.2), whereas little increased risk was seen among white men who never married (OR = 1.2; 0.6–2.5).
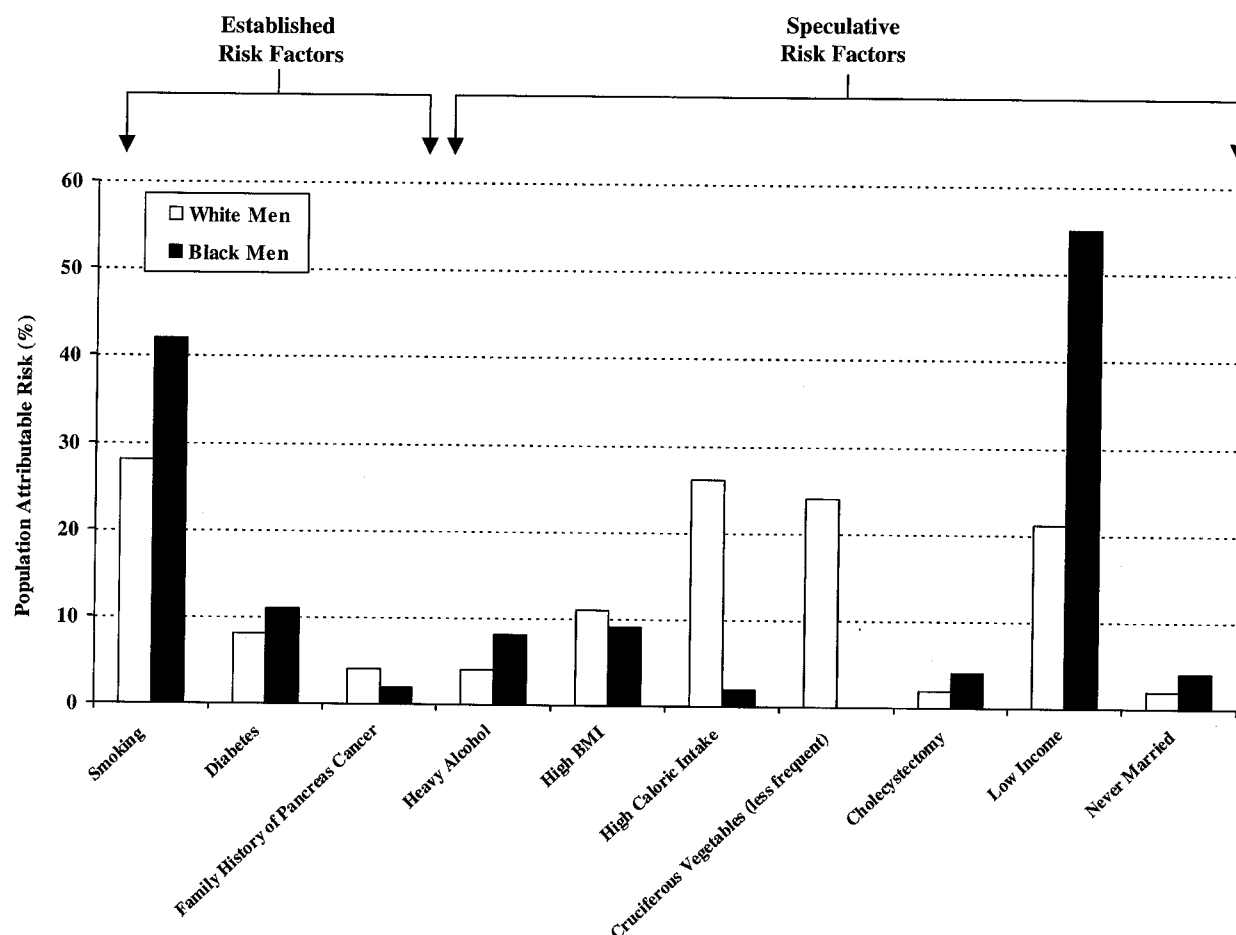
FIGURE 1.   Population attributable risks for pancreatic cancer risk factors among men, by race.

Among women, income was only weakly related to risk. Black women with an annual family income of $10,000–$24,999 had an OR of 1.3 (CI = 0.6–3.0) whereas white women with an annual income of less than $10,000 had an OR of 1.3 (0.6–2.7), but no trend in risk with decreasing income was apparent in blacks or whites. Education did not appear related to risk among black or white women. Those who were widowed, separated or divorced had elevated risks, which were more pronounced in black women (OR = 1.9; 1.1–3.3) than in white women (OR = 1.2; 0.7–2.0).

Population Attributable Risks for Individual Risk Factors

To identify the individual risk factors that contribute to the black excess, we estimated the PAR for each risk factor (Figures 1 and 2). The main factors that contributed to the excess risk of pancreatic cancer among black men were: cigarette smoking, diabetes mellitus, heavy alcohol drinking and low income (Figure 1). For smoking, the PAR was 42% in black men and 28% in white men. The percentage of male controls who ever smoked

cigarettes was similar in blacks and whites (70% and 69%, respectively), but the estimate of risk was higher for blacks than whites (OR = 2.0 and 1.6) (Table 2). For diabetes, the PAR was 12% in black men and 7% in white men. The ORs were similar in blacks and whites (2.3 and 2.1, respectively), but 11% of black controls had diabetes compared with 6% of white controls (Table 2). For heavy alcohol drinking (more than 56 drinks per week), the PAR was 8% for black men and 4% for white men. Blacks experienced both a higher risk associated with heavy drinking than whites (OR = 2.2 and 1.4), and a higher proportion of black controls than white controls were heavy drinkers (8% and 5%) (Table 2). For low income, the PAR was 55% in black men and 22% in white men. This difference reflects both the higher proportion of low-income black controls than white controls, as well as the higher pancreatic cancer risk associated with low income for blacks compared with whites. Seventy percent of black controls had an annual income of less than $25,000 compared with 42% of white controls, although the ORs for pancreatic cancer were higher for black men than white men at each
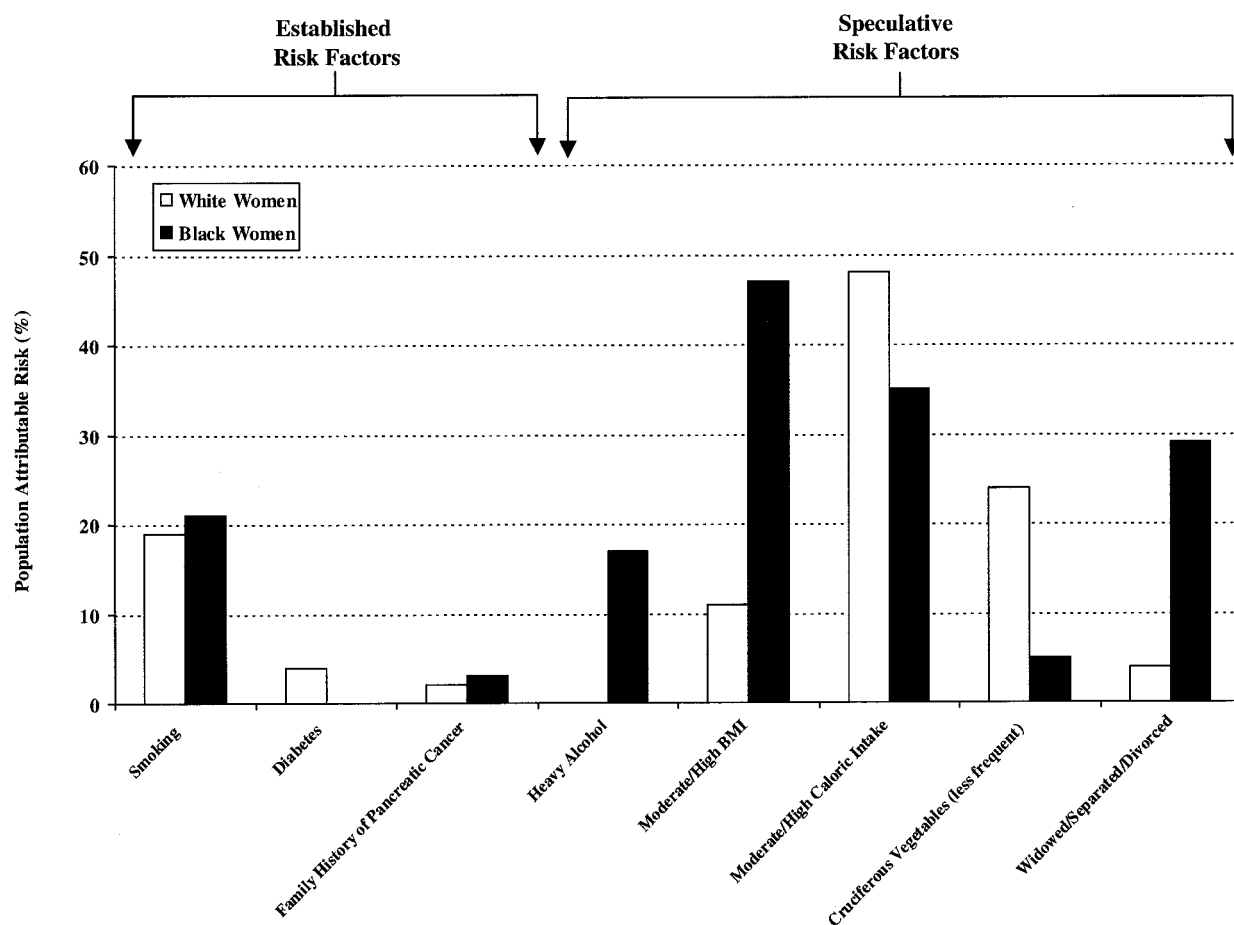
FIGURE 2.   Population attributable risks for pancreatic cancer risk factors among women, by race.

level of income (Table 2). Cholecystectomy and never-married status contributed only slightly to the excess risk among blacks, with PARs for each factor being less than 5% for men of both races.

The PARs for individual risk factors for black and white women are shown in Figure 2. Among women, the key

contributors to the black excess in risk were: moderate/heavy alcohol drinking, moderate/high BMI and marital status of widowed, separated or divorced. For moderate/heavy alcohol drinking, the PAR was 17% for black women and 0% for white women. This difference reflects the elevated risk associated with moderate/heavy drinking

TABLE 2.   Association of Various Risk Factors with Pancreatic Cancer, by Sex and Race

Risk Factor	White			Black		
	OR*	95% CI	Percent of Controls Exposed	OR*	95% CI	Percent of Controls Exposed
Men						
Cigarette smoking	1.6	1.0–2.5	69	2.0	1.0–4.2	70
Heavy alcohol intake†	1.4	0.6–3.2	5	2.2	0.9–5.6	8
Diabetes mellitus	2.1	1.1–3.8	6	2.3	1.1–4.7	11
Low income‡	1.8	0.9–3.4	42	2.7	1.2–6.1	70
Women						
Moderate/heavy alcohol intake†	0.8	0.4–1.6	15	2.1	1.1–3.8	17
Moderate/high BMI	1.2	0.7–2.0	70	2.1	1.0–4.6	81
Marital status of widowed, separated, divorced	1.2	0.7–2.0	31	1.9	1.1–3.3	53

BMI = Body Mass Index.
* ORs were adjusted for age at diagnosis/interview, study area, cigarette smoking, heavy alcohol drinking, diabetes mellitus, cholecystectomy, obesity, total caloric intake, cruciferous vegetable intake, income and marital status.
† Heavy alcohol intake was ≥57 drinks/week for men and moderate/heavy alcohol intake was ≥8 drinks/week for women.
‡ Low income was <$25,000/year at the time of the interview.

TABLE 3. Population Attributable Risk (PAR) for Established Risk Factors* and Other Factors That Contribute to Excess Risk of Pancreatic Cancer Among Blacks†

Race/Sex	PAR (%)	95% CI	Total Pancreatic Cancer Incidence Rate (per 100,000)	Pancreatic Cancer Incidence Rate in Nonexposed‡ (per 100,000)
Established risk factors§				
Men				
White	37	13 to 62	12.8	8.1
Black	46	10 to 82	16.0	8.6
Women				
White	27	4 to 49	9.0	6.6
Black	15	−13 to 43	13.3	11.3
Established risk factors in combination with other factors that contribute to the black excess in risk‖				
Men				
White	49	23 to 74	12.8	6.5
Black	53	13 to 93	16.0	7.5
Women				
White	47	2 to 92	9.0	4.8
Black	88	66 to 111	13.3	1.6

* Established risk factors: ever smoked cigarettes, diabetes mellitus (for at least 5 years), and family history of pancreatic cancer.
† Other factors that contribute to excess risk in blacks are moderate/heavy alcohol drinking (men: ≥57 drinks/week; women: ≥8 drinks/week), and moderate/high body mass index (men: top quartile; women: top 3 quartiles).
‡ Obtained by applying the proportion of disease not explained by these risk factors (complement of PAR) to the total pancreatic cancer incidence rate.
§ All PARs were adjusted for age at diagnosis/interview, study area, alcohol drinking, cholecystectomy (at least 5 years before pancreatic cancer), body mass index, total caloric intake (men: top quartile; women: top 3 quartiles), cruciferous vegetable consumption (<5 times/week), income (<$25,000/year) and marital status (men: never married; women: widowed, separated, divorced). Nonexposed includes only subjects who were nondiabetic nonsmokers with no family history of pancreatic cancer.
‖ Heavy alcohol intake and high BMI were the additional variables included. All PARs were adjusted for age at diagnosis/interview, study area, cholecystectomy, total caloric intake, cruciferous vegetable consumption, income and marital status. Nonexposed includes: Men: only nondiabetic, nonsmoking men with no family history of pancreatic cancer who were not in the top body mass index (BMI) quartile and who drank 0–56 drinks/week; Women: only nondiabetic, nonsmoking women with no family history of pancreatic cancer who were in the lowest BMI quartile and who drank 0–7 drinks/week.

among black women, but not among white women in our study (OR = 2.1 and 0.8, respectively), because a similar percentage of black and white female controls were moderate/heavy drinkers (17% and 15%) (Table 2). For BMI, the PAR was 47% for black women and only 11% for white women. This large disparity is attributable to both a higher percentage of black controls than white controls in the top three quartiles of BMI (81% and 70%) and a higher risk for black women than white women in the top three quartiles (OR = 2.1 and 1.2) (Table 2). For marital status, the PAR for being widowed, separated or divorced was 29% for black women and only 4% for white women. This difference is attributable to both a higher percentage of black controls than white controls in this category (53% and 31%) and a higher pancreatic cancer risk in black women compared with white women (OR = 1.9 and 1.2) (Table 2). Diabetes, although more prevalent among black than white women, did not appear to contribute to the excess risk among black women because the OR for black women was 0.6 (CI = 0.2–1.3) compared with 1.8 (0.8–4.2) for white women. Because 94% of the black women with diabetes in our study were in the top three quartiles of BMI, the PAR for diabetes is subsumed below in the summary PARs for combined risk factors including BMI.

Summary Population Attributable Risks

Table 3 shows summary PARs both for established risk factors (*ie*, the combination of ever smoked cigarettes, long-term diabetes, and history of pancreatic can-

cer in a first-degree relative), and for established risk factors combined with two speculative risk factors that contributed to the excess among blacks in our study (*ie*, heavy alcohol intake and high BMI). Among men, the PAR for established risk factors was 46% in blacks and 37% in whites. The total age-adjusted incidence rate for pancreatic cancer for the three areas combined during the study period was 16.0/100,000 in black men and 12.8/100,000 in white men, yielding a 25% excess risk in blacks. The complement of the PAR, the proportion of the disease not explained by established risk factors, was applied to the total incidence rate to estimate the incidence in men who were not exposed to established risk factors (*ie*, nondiabetic nonsmokers with no family history of pancreatic cancer). In the absence of established risk factors, pancreatic cancer incidence rates would have been 8.6/100,000 for black men and 8.1/100,000 for white men, yielding a 6% excess in blacks. When heavy alcohol drinking and high BMI were taken together with the established risk factors, the summary PAR was 53% for black men and 49% for white men. In the absence of heavy alcohol drinking, high BMI and established risk factors, pancreatic cancer incidence rates would have been 7.5/100,000 for black men and 6.5/100,000 for white men, yielding a 15% higher risk in blacks. When low income (*ie*, less than $25,000 per year) and marital status of "never married" were combined with heavy alcohol drinking, high BMI and established risk factors (data not shown), the summary PAR

was 76% for black men and 71% for white men. In the absence of these factors, pancreatic cancer incidence rates would have been nearly identical in black and white men (3.8/100,000 and 3.7/100,000, respectively).

Among women, established risk factors did not appear to contribute to the black excess in risk (Table 3). The summary PAR for known risk factors was 15% in black women and 27% in white women. The total age-adjusted incidence rate for the three study areas was 13.3/100,000 in black women and 9.0/100,000 in white women, yielding a 48% excess risk in blacks. In the absence of established risk factors, pancreatic cancer incidence rates would have been 11.3/100,000 in black women and 6.6/100,000 in white women, yielding a 71% higher risk in blacks. When heavy alcohol drinking and moderate/high BMI were taken together with known risk factors, the summary PAR was 88% in black women and 47% in white women. In the absence of heavy drinking, moderate/high BMI and established risk factors, incidence rates would have been 1.6/100,000 for black women and 4.8/100,000 for white women, yielding a higher risk among white women. When low income (less than $25,000 per year) and marital status of widowed, separated or divorced were combined with heavy drinking, elevated BMI and established risk factors (data not shown), virtually all of the disease in black women and about half of the disease in white women could be explained by this combination of factors. This observation, however, is based on a small number of black women (94 cases, 347 controls).

Discussion

Our findings indicate that the determinants of the higher incidence of pancreatic cancer among blacks than among whites in the United States vary by sex. Among men, established risk factors (ie, cigarette smoking, diabetes mellitus and family history of pancreatic cancer) explained all but 6% of the excess risk among blacks. When these factors were taken together with speculative or less accepted factors (ie, heavy alcohol consumption, elevated BMI and low socioeconomic status), it was possible to account entirely for the differential incidence between black and white men. Among women, however, established risk factors account for little of the racial disparity in incidence, which was explained only by factoring in speculative risk factors.

Our population-based case-control study is the first analytic investigation designed to identify factors responsible for the elevated incidence of pancreatic cancer among blacks in the United States. Despite the large size of this study, our observations were often based on racial differences in population attributable risk that had wide confidence intervals, although they appeared to be meaningful because of their scientific plausibility. These

findings will require confirmation in future studies. The generalizability of our findings to other populations will depend on two factors: the magnitude of risk associated with established/speculative risk factors and the prevalence of these risk factors in a given population. It is noteworthy that our study population consisted of residents of mainly urban areas (ie, Detroit, Atlanta and 10 counties in New Jersey) from 1986 to 1989. Exposures to explanatory variables among blacks and whites in our study may differ from those in the general U.S. population of today, limiting the generalizability of our findings.

We used the PAR to quantify the proportion of the black excess that may be attributable to a particular risk factor or group of risk factors. Because the PAR is dependent on the definition of exposure, our approach was to estimate the PAR for both "established" and "established plus speculative" risk factors, determining the likely range of the PAR. We defined "established" risk factors as those exposures that are known causes of pancreatic cancer. In contrast, "speculative" risk factors are those exposures that have been linked to pancreatic cancer in several previous studies but have not warranted a causal interpretation. "Speculative" risk factors were selected by virtue of elevated ORs in this study or exposure prevalences in the population controls that might contribute to excess risk among blacks.

The established risk factors for pancreatic cancer in our study included cigarette smoking, which has been convincingly identified by at least 30 epidemiologic studies.[1,19–21] In addition, the risk we observed with diabetes is consistent with a meta-analysis indicating that long-standing diabetes is a risk factor for pancreatic cancer rather than a complication of the disease.[22] Furthermore, the familial tendency to pancreatic cancer in our study is consistent with clinical surveys and with case-control studies in the United States,[23] Canada[24] and Italy[25] that have indicated an approximately three-fold risk associated with a positive family history.

The "speculative" risk factors included heavy alcohol intake, elevated BMI and low socioeconomic status. The excess risk associated with heavy drinking in our study, particularly among blacks,[7] is consistent with at least eight previous studies,[26–34] although such an effect has not been seen in other studies.[35–43] Obesity was associated with elevated risk in our study,[8] as well as in others, with relative risks ranging from 1.2 to 1.7 in some case-control investigations from the United States[44,45] and China,[46] and in cohort studies from the United States[47,48] and Denmark.[49] In contrast, a multinational case-control study of pancreatic cancer[50–52] and some case-control studies in the United States[53–55] and Greece[56] have revealed no clear relation to BMI.

Evidence that low socioeconomic status is a risk factor for pancreatic cancer is equivocal.[57,58] The elevated

risk we observed with low socioeconomic status is supported by some studies,[59–65] but not by several others.[23,66–78] Although it has been suggested that the excess of pancreatic cancer among blacks might be attributable to socioeconomic status–related factors[79] such as smoking, heavy alcohol drinking and dietary factors, our study revealed independent effects of low income in men and marital status in men (never married) and women (widowed, separated, divorced). These variables were associated with increased risk after adjustment for the confounding effects of smoking, heavy drinking and dietary/nutritional factors. Although few studies have linked pancreatic cancer to low income[58] or marital status,[80,81] it is noteworthy that their effects in our study differed by race and sex for reasons that are unclear. Socioeconomic status is a different type of variable than a direct exposure variable such as cigarette smoking. Rather, socioeconomic status is a marker for exposures related to lifestyle. In the current analysis, inclusion of socioeconomic status in the PAR models more fully explains the racial disparity in risk, particularly in women. If the observed associations with low income and marital status reflect real differences in risk, these observations could help focus the search for unidentified risk factors that are socioeconomic in nature rather than racial in origin. For example, low socioeconomic effects may be attributable to increased exposure to infectious agents or nutritional deficiencies that were not examined in the present study.

Although income and marital status may be surrogates for other risk factors, it is also possible that reporting or response bias may be operating. Response bias appears unlikely, however, for a number of reasons. First, cooperation rates among those approached for interview were similar in cases and controls, which would have resulted in a dilution of effect in the presence of response bias. Second, a comparison of the distribution of annual family income reported by our population controls with that from 1990 census data[82] for the three study areas for the relevant age groups revealed that, if anything, response bias could have resulted in an underestimation of the OR for low income. We found that low-income (<$10,000 per year) blacks seem overrepresented and higher-income (≥$25,000 per year) blacks underrepresented among the black controls. In contrast, low-income whites were accurately represented (at 10% of the control group compared with 11% of the census population), but higher-income whites were underrepresented among the white controls. Third, response bias would have been introduced if there was a survival bias, because a substantial proportion of the cases died before interview—but in fact, directly interviewed cases and next of kin of deceased cases reported similar income distributions.

Cigarette smoking is the only risk factor for which the PAR estimate for pancreatic cancer has been replicated in several studies. Our PAR estimate of 27% for smoking[6] is consistent with previous estimates ranging from 14% to 35%.[19,20,54,83,84] In understanding any multifactorial disease, however, it is critical to evaluate the PAR for all known exposures. The sum of PARs for individual factors may exceed 100%, whereas the summary PAR for all risk factors combined will not exceed 100%. However, only one previous study of pancreatic cancer has examined attributable risks for multiple exposures. A case-control study in Greater Milan reported that a "few selected risk factors" (*ie*, cigarette smoking, high meat consumption and low fruit intake) explained 23% of the disease.[84] A number of the factors implicated in our study, including diabetes, BMI and socioeconomic status, were not considered in the estimation of attributable risks in the Italian study.

In conclusion, the excess incidence among blacks in our study population was explained by established risk factors (mainly cigarette smoking and diabetes) in men and less accepted risk factors (*ie*, heavy alcohol drinking and elevated BMI) in women. The higher PARs in blacks compared with whites for some exposures such as elevated BMI were attributable, at least in part, to the higher prevalence of exposure in blacks. From a public health perspective, intervention programs aimed at smoking cessation and reducing excess weight would have a disproportionately beneficial effect on pancreatic cancer reduction in blacks. For other exposures such as moderate/heavy alcohol consumption in women, however, blacks experienced higher risks than whites at the same levels of exposure. Although these findings may be attributable to chance, it is possible that blacks are more susceptible because of genetic variations in the metabolism of some carcinogens. Molecular epidemiologic studies will be needed to identify the gene-environment interactions that may explain racial disparities in the incidence of pancreatic cancer.

References

1. Anderson KE, Potter JD, Mack TM. Pancreatic cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention.* New York: Oxford University Press, 1996;725–771.
2. Ries LAG, Eisner MP, Kosary CL, *et al.*, eds. *SEER Cancer Statistics Review, 1973–1999.* Bethesda: National Cancer Institute, 2002.

3. Kovi J, Heshmat MY. Incidence of cancer in Negroes in Washington, DC and selected African cities. *Am J Epidemiol* 1973;96: 401–413.

4. Walker ARP, Walker BF, Segal I. Cancer patterns in three African populations compared with the United States Black population. *Eur J Cancer Prev* 1993;2:313–320.

5. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds. *Cancer Incidence in Five Continents. Vol. VII.* Lyon, France: IARC Scientific Publications No. 143, 1997.

6. Silverman DT, Dunn J, Hoover R, et al. Cigarette smoking and pancreas cancer: a case-control study based on direct interviews. *J Natl Cancer Inst* 1994;86:1510–1516.

7. Silverman DT, Brown LM, Hoover RN, et al. Alcohol and pancreatic cancer in blacks and whites in the United States. *Cancer Res* 1995;55:4899–4905.

8. Silverman DT, Swanson CA, Gridley G, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J Natl Cancer Inst* 1998;90:1710–1719.

9. Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer* 1999;80:1830–1837.

10. Silverman DT, Schiffman M, Devesa SS. Diagnostic certainty in pancreatic cancer. *J Clin Epidemiol* 1996;49:601–603.

11. McLaughlin JK, Mandel JS, Mehl ES, Blot WJ. Comparison of next-of-kin with self-respondents regarding questions on cigarette, coffee and alcohol consumption. *Epidemiology* 1990;1:408–412.

12. Gavalda L, Porta M, Malats N, et al. Concordancia entre la informacion facilitada por el paciente y un familiar sobre antecedentes patologicos, consumo de tabaco, de alcohol, de café, y dieta en el cancer de pancreas exocrino y del sistem biliar extrahepatico. *Gac Sanit* 1995;9:334–342.

13. Waksberg J. Sampling methods for random digit dialing. *J Am Stat Assoc* 1978;73:40–46.

14. Micozzi MS, Albanes D, Jones DY, Chumlea WC. Correlations of body mass indices with weight, stature, and body composition in men and women in NHANES I and II. *Am J Clin Nutr* 1986;44: 725–731.

15. Breslow NE, Day NE. Analysis of Case-Control Studies. In: *Statistical Methods in Cancer Research. Vol. I.* Lyon, France: IARC Scientific Publications, 1980.

16. Dixon WJ, Brown MB, Engelmen L, Jennrick RI, eds. *BMDP Statistical Software Manual, Vol. II.* Berkeley: University of California Press, 1990.

17. Bruzzi P, Green SB, Byar DP, Brinton LA. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol* 1985;122:904–914.

18. Benichou J, Gail MH. Variance calculations and confidence intervals for estimates of the attributable risk based on logistic models. *Biometrics* 1990;46:991–1003.

19. Ji BT, Chow WH, Dai Q, et al. Cigarette smoking and alcohol consumption and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Cancer Causes Control* 1995;6:369–376.

20. Fuchs CS, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med* 1996;156:2255–2260.

21. Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: The Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev* 1997;6:1081–1086.

22. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. *JAMA* 1995;273:1605–1609.

23. Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF Jr. Lifestyle factors for pancreatic cancer in Louisiana: a case-control study. *Am J Epidemiol* 1988;128:324–36.

24. Ghadirian P, Boyle P, Simard A, Baillargeon J, Maisonneuve P, Perret C. Reported family aggregation of pancreatic cancer within a population-based case-control study in the Francophone community in Montreal, Canada. *Int J Pancreatol* 1991;10:183–196.

25. Fernandez E, La Vecchia C, D'Avanzo B, Negri E, Franceschi S. Family history and the risk of liver, gallbladder, and pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 1994;3:209–212.

26. Hakulinen T, Lehtimaki L, Lehtonen M, Teppo L. Cancer morbidity among two male cohorts with increased alcohol consumption in Finland. *J Natl Cancer Inst* 1974;52:1711–1714.

27. Adelstein A, White G. Alcoholism and mortality. *Popul Trends* 1976;6:7–13.

28. Klatsky AL, Friedman GD, Siegelaub AB. Alcohol and mortality: a ten-year Kaiser-Permanente experience. *Ann Intern Med* 1981; 95:139–145.

29. Heuch I, Kvale G, Jacobsen BK, Bjelke E. Use of alcohol, tobacco and coffee and risk of pancreatic cancer. *Br J Cancer* 1983;48:637–643.

30. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gallbladder disease. *Int J Cancer* 1989;43:415–421.

31. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. *Am J Public Health* 1989;79:1016–1019.

32. Adami HO, McLaughlin JK, Hsing AW, et al. Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control* 1992;3:419–425.

33. Tonnesen H, Moller H, Anderson JR, et al. Cancer morbidity in alcohol abusers. *Br J Cancer* 1994;69:327–332.

34. Partanen TJ, Vainio HU, Ojajarvi IA, et al. Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: a case-control study. *Cancer Lett* 1997;116:27–32.

35. Sundby P. *Alcoholism and Mortality.* Oslo, Norway: Universitetsforlaget, 1967.

36. Schmidt W, de Lint J. Causes of death of alcoholics. *J Stud Alcohol* 1972;33:171–185.

37. Monson RR, Lyon JL. Proportional mortality among alcoholics. *Cancer* 1975;36:1077–1079.

38. Dean G, MacLennan R, McLoughlin H, Shelley E. Causes of death of blue-collar workers at a Dublin brewery, 1954–73. *Br J Cancer* 1979;40:581–589.

39. Robinette CD, Hrubec Z, Fraumeni JF Jr. Chronic alcoholism and subsequent mortality in World War II veterans. *Am J Epidemiol* 1979;109:687–700.

40. Jensen OM. *Cancer Morbidity and Causes of Death Among Danish Brewery Workers.* Lyon, France: IARC, 1980.

41. Schmidt W, Popham RE. The role of drinking and smoking in mortality from cancer and other causes in male alcoholics. *Cancer* 1981;47:1031–1041.

42. Tavani A, Pregnolato A, Negri E, La Vecchia C. Alcohol consumption and risk of pancreatic cancer. *Nutr Cancer* 1997;27:157–161.

43. Talamini G, Bassi C, Falconi M, et al. Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer. *Dig Dis Sci* 1999;44:1303–1311.

44. Friedman GD, van den Eeden SK. Risk factors for pancreatic cancer: an exploratory study. *Int J Epidemiol* 1993;22:30–37.

45. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. *Int J Cancer* 1994;58:46–49.

46. Ji BT, Hatch MC, Chow WH, et al. Anthropometric and reproductive factors and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Int J Cancer* 1996;66:432–437.

47. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control* 2000;11:915–923.

48. Michaud DS, Giovannucci E, Willett WC, et al. Prospective study of physical activity, obesity, height and the risk of pancreatic cancer. *JAMA* 2001;286:921–929.

49. Moller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. *Euro J Cancer* 1994; 30A:344–350.

50. Bueno de Mesquita HB, Moerman CJ, Runia S, Maissonneuve P. Are energy and energy-providing nutrients related to exocrine carcinoma of the pancreas? *Int J Cancer* 1990;46:435–444.

51. Ghadirian P, Simard A, Baillargeon J, Maissonneuve P, Boyle P. Nutritional factors and pancreatic cancer in the francophone community in Montreal, Canada. *Int J Cancer* 1991;47:1–6.

52. Howe GR, Ghadirian P, Bueno de Mesquita HB *et al*. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. *Int J Cancer* 1992;51:365–372.

53. Lyon JL, Slattery ML, Mahoney AW, Robinson LM. Dietary intake as a risk factor for cancer of the exocrine pancreas. *Cancer Epidemiol Biomarkers Prev* 1993;2:513–518.

54. Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst* 1986;76:49–60.

55. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. Nutrients and pancreatic cancer: a population-based case-control study. *Cancer Causes Control* 1991;2:291–297.

56. Kalapothaki V, Tzonou A, Hsieh CC, *et al*. Nutrient intake and cancer of the pancreas: a case-control study in Athens, Greece. *Cancer Causes Control* 1993;4:383–389.

57. Van Loon AJ, Brug J, Goldbohm RA. Differences in cancer incidence and mortality among socio-economic groups. *Scand J Soc Med* 1995;23:110–120.

58. Kogevinas M, Pearce N, Susser M, Boffetta P, eds. *Social Inequalities and Cancer*. Lyon, France: IARC Scientific Publications No. 138, 1997.

59. HM Stat Office. *Registrar General's Decennial Supplement for England and Wales, 1931. Occupational Mortality*. London: HM Stat Office, 1938.

60. Cohart EM, Muller C. Socioeconomic distribution of cancer of the gastrointestinal tract in New Haven. *Cancer* 1955;8:1126–1129.

61. Dorn HF, Cutler SJ. Morbidity from cancer in the United States. Part II. Trend in morbidity association with income and stage at diagnosis. *Public Health Monogr* 1958;56;106.

62. Krain LS. The rising incidence of cancer of the pancreas. Further epidemiologic studies. *J Chronic Dis* 1971;23:685–690.

63. Krain LS. Cancer of the pancreas in California, 1942–1967. *Calif Med* 1971;115:38–41.

64. Seidman H. Cancer death rates by site and sex for religious and socioeconomic groups in New York City. *Environ Res* 1970;3:234–250.

65. Young JL, Devesa SS, Cutler SJ. Incidence of cancer in United States blacks. *Cancer Res* 1975;35:3523–3526.

66. HM Stat Office. *Registrar General's Decennial Supplement for England and Wales, 1951. Occupational Mortality Tables, Part 1*. London: HM Stat Office, 1954.

67. Graham S, Levin M, Lilienfeld AM. The socioeconomic distribution of cancer of various sites in Buffalo, NY: 1948–1952. *Cancer* 1960;13:180–190.

68. Moldow RE, Connelly RR. Epidemiology of pancreatic cancer in Connecticut. *Gastroenterology* 1968;55:667–686.

69. Levin DL, Connelly RR. Cancer of the pancreas. *Cancer* 1973;31: 1231–1236.

70. Wynder EL, Mabuchi K, Maruchi N, *et al*. A case-control study of cancer of the pancreas. *Cancer* 1973;31:641–648.

71. Williams RR, Horm JW. Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: interview study from the Third National Cancer Survey. *J Natl Cancer Inst* 1977;58:525–547.

72. Blot WJ, Fraumeni JF Jr, Stone BJ. Geographic correlates of pancreas cancer in the United States. *Cancer* 1978;42:373–380.

73. Levin DL, Connelly RR, Devesa SS. Demographic characteristics of cancer of the pancreas: mortality, incidence, and survival. *Cancer* 1981;47:1456–1468.

74. Lin RS, Kessler II. A multifactorial model for pancreatic cancer in man. *JAMA* 1981;245:147–152.

75. Mack TM, Paganini-Hill A. Epidemiology of pancreas cancer in Los Angeles. *Cancer* 1981;47:1474–1483.

76. Logan WPD. Cancer mortality by occupation and social class 1851–1971. *OPCS, Studies on Medical and Population Subjects No. 44*. Lyon, France: IARC Scientific Publication No. 36, 1982.

77. Wynder EL, Hall NEL, Polansky M. Epidemiology of coffee and pancreatic cancer. *Cancer Res* 1983;43:3900–3906.

78. Ferraroni M, Negri E, La Vecchia C, *et al*. Socioeconomic indicators, tobacco and alcohol in the aetiology of digestive tract neoplasms. *Int J Epidemiol* 1989;18:556–562.

79. McWhorter WP, Schatzkin AG, Horm JW, Brown CC. Contribution of socioeconomic status to black/white differences in cancer incidence. *Cancer* 1989;63:982–987.

80. Swanson GM, Belle SH, Satariano WA. Marital status and cancer incidence: differences in the black and white populations. *Cancer Res* 1985;45:5883–5889.

81. Kato I, Tominaga S, Terao C. An epidemiological study on marital status and cancer incidence. *Jpn J Cancer Res* 1989;80: 306–311.

82. U. S. Census Bureau. *1990 Census Lookup*. Available at: http://homer.ssd.census.gov/cdrom/lookup. 1990 Census Summary Tape File 3A, Sample count - all socioeconomic and demographic variables by detailed geography - county. Race of householder (1) by age of householder (7) by household income in 1989 (9); Universe: white households (P87A); Universe: black households (P87B).

83. United States Office of Smoking and Health. *Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General*. Rockville, MD: Department of Health and Human Services, Publication No. (CDC) 89–8411, 1989.

84. Fernandez E, La Vecchia C, Decarli A. Attributable risks for pancreatic cancer in northern Italy. *Cancer Epidemiol Biomarkers Prev* 1996;5:23–27.